Physiology of muscle contraction
Learning objectives 21-24
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Types:
- Smooth muscle
- Cardiac muscle
- Skeletal muscle
  - cross-striation
  - nervous stimulation induces contraction
  - voluntary control
  - lack of anatomical connections of individual muscle fibres

Muscle contracts and relaxes → Body moves and transports
- respiration
- heart/circulation
- gastrointestinal tract
Muscle tissue accounts for almost half of the human body mass.

Topics:
Skeletal muscle (ca. 400 muscles)
  Structure
  Muscle contraction
    Excitation-contraction coupling
    Energetic of muscle contraction
    Mechanics of muscle contraction
Smooth muscle - compared to skeletal muscle
Muscle fiber

Thick filament: MYOSIN contractile proteins
Thin filament: ACTIN TROPOMYOSIN TROPONIN regulatory proteins
α-Aktinin Titin structure proteins

Relaxed

Contracted
Diagram of muscle cell membrane (sarcolemma), dystrophin, and the dystrophin-associated protein complex. Dystrophin is located inside the cell and binds actin at its N-terminus and the syntrophins, sarcoglycans, and dystrobrevin at the C-terminus. Mutations in dystrophin are responsible for Duchenne muscular dystrophy.
Components of the thin filament

- **Troponin subunits**
  - TnI: holds the tropomyosin over the active sites on actin
  - TnC: binds Ca$^{2+}$
  - TnT: binds to tropomyosin

(a) Myosin binding sites blocked; muscle cannot contract

(b) Myosin binding sites exposed; muscle can contract
Sliding filament mechanism


Motor unit

Dying Lioness, ca. 650 B.C.
Palace of Ashurbanipal at Ninevah
Electromyography (EMG) is a technique for evaluating and recording the electrical activity produced by skeletal muscles when they are activated.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Activity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>resting</td>
<td>Low</td>
</tr>
<tr>
<td>slight contraction</td>
<td>Moderate</td>
</tr>
<tr>
<td>moderate contraction</td>
<td>High</td>
</tr>
<tr>
<td>maximal contraction</td>
<td>Very High</td>
</tr>
</tbody>
</table>

**Neuromuscular junction**

- myelin sheath
- axon of the motoneuron
- Schwann cell
- terminal buttons
- muscle
- motor end-plate
- active zone
- junctional folds
- muscle
The Neuromuscular Junction

**Neuromuscular blockade**

- **Inhibition of ACh release**
  - Botulinum toxin
  - Drugs inhibiting the binding of ACh to its receptor
    - Curare
  - Drugs inhibiting acetylcholinesterase
    - reversible inhibitor: Neostigmine
    - irreversible inhibitor: Organophosphates (insecticides), Nerve gases

**Myasthenia gravis**: Autoantibodies directed against ACh receptors
Excitation-contraction coupling

Depolarisation induces opening of Ca\(^{2+}\) channels

Molecular basis of contraction
Formation of cross-bridges
Excitation-contraction coupling

Depolarisation induces opening of Ca\(^{2+}\) channels

SERCA: Sarcoplasm-endoplasma reticulum ATP-ase
Molecular basis of contraction
Formation of cross-bridges

1. **Z-line** dissociation
2. **ATP** is hydrolyzed
3. **Ca^{2+}** release
4. **Ca^{2+}** reuptake
5. **Power stroke**
6. ATP regeneration

- **Mg^{2+}-dependent ATPase**
- 5 cycles/sec

Symbols:
- ATP
- **Ca^{2+}
- **Mg^{2+}
Source of energy for skeletal muscle contraction

ATP

Creatine phosphate
Creatine phosphate + ADP ⇌ Creatine + ATP

Carbohydrate and Lipid breakdown
Free fatty acids, Glucose, Glycogen
- anaerobic (production of lactic acid)
- aerobic (myoglobin)

Myoglobin is a monomeric heme protein found in muscle tissue where it serves as an intracellular storage site for oxygen. During periods of oxygen deprivation oxymyoglobin releases its bound oxygen which is then used for metabolic purposes.

Source of energy

<table>
<thead>
<tr>
<th>Event</th>
<th>Duration</th>
<th>Energy Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-m dash</td>
<td>10 sec</td>
<td>85% anaerobic</td>
</tr>
<tr>
<td>3-km race</td>
<td>10 min</td>
<td>20% anaerobic</td>
</tr>
<tr>
<td>long-distance race</td>
<td>60 min</td>
<td>5% anaerobic</td>
</tr>
</tbody>
</table>
### Types of muscle fibres

<table>
<thead>
<tr>
<th></th>
<th>Type I.</th>
<th>Type II.</th>
<th>Type II.a</th>
<th>Type II.b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow-oxidative</td>
<td>Fast-oxidative/ glycolytic</td>
<td>Fast-glycolytic</td>
<td></td>
</tr>
<tr>
<td>mitochondria</td>
<td>many</td>
<td>many</td>
<td>few</td>
<td></td>
</tr>
<tr>
<td>capillaries</td>
<td>many</td>
<td>many</td>
<td>few</td>
<td></td>
</tr>
<tr>
<td>myoglobin content</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>myosin ATPase activity</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>contraction velocity</td>
<td>slow</td>
<td>fast</td>
<td>fast</td>
<td></td>
</tr>
<tr>
<td>rate of fatigue</td>
<td>slow</td>
<td>intermediate</td>
<td>fast</td>
<td></td>
</tr>
<tr>
<td>muscle fiber diameter</td>
<td>small</td>
<td>intermediate</td>
<td>large</td>
<td></td>
</tr>
<tr>
<td>innervating neuron size</td>
<td>small</td>
<td>intermediate</td>
<td>large</td>
<td></td>
</tr>
<tr>
<td>motor unit size</td>
<td>small</td>
<td>intermediate</td>
<td>large</td>
<td></td>
</tr>
</tbody>
</table>

Michael Phelps - the most decorated Olympian ever

Genetic variants associated with over 200 genes are documented to affect athletic performance. They affect a variety of functions including blood flow to muscles, muscle structure, oxygen transport, lactate turnover, and energy production.
**Muscle fatigue**

Depletion of ATP  
Acidic pH in the muscle (lactic acid)  
Depletion of ACh  
+ psychological fatigue

**Heat production in muscle:** efficacy of the muscle contraction is 20-30%

Thermogenesis: shivering  
voluntary contraction

**Rigor mortis**

Lack of ATP!

**Contracture** – contraction without AP  
**Muscle soreness**

Androgen hormones, growth hormone – anabolic effect (doping) 😞
Muscle fiber action potential

Muscle fiber shortening

Temporal relationships between AP, Ca^{2+} signal and muscle contraction
Factors increasing the force of muscle contraction:

1) Motor unit: frequency of AP ↑
2) Recruitment of motor units

The size principle: when a muscle contracts against a load, the smallest motor units (which have only a few muscle fibres in them) are recruited first. If the force generated is insufficient, then the larger motor units are recruited.
Types of muscle contraction
result of muscle contraction

**ISOTONIC CONTRACTION**
("same tension")

**ISOMETRIC CONTRACTION**
("same length")

**AUXOTONIC CONTRACTION**
Most contractions in daily life show some change in length and some change in tension; these are called auxotonic.

Length – tension relationship

**Isotonic contraction**
- Passive tension: produced by titin
- Active tension: force generated by the deformation of myosin heads

**Isometric contraction**
- Passive tension
Length – active tension relationship in skeletal muscle fibres

Smooth muscle
Contracts to 30% of its initial length (skeletal muscle contracts to 60% of its initial length)

Mechanism of smooth muscle contraction

MLCK: Myosin light chain kinase

MLCP: Myosin light chain phosphatase

It does not contain troponin!
Action potential
Voltage-gated Ca\(^{2+}\)-channel
Ligand-gated Ca\(^{2+}\)-channel
catecholamines
\(\alpha_1\)-receptor

Activation

Relaxation

Electromechanical coupling
Pharmacomechanical coupling

smooth muscle

Ca\(^{2+}\)-induced Ca\(^{2+}\) release

\(\text{RyR: Ryanodine Receptor}\)

Regulation of \(\text{Ca}^{2+}\)-sensitivity"

\(\text{Ca}^{2+}\)-desensitization
Phosphorylation of Myosin light chain
tension

\(\text{Ca}^{2+}\)-sensitization
Phosphorylation of Myosin light chain
tension

Myosin light chain kinase
MLCK

Myosin light chain phosphatase
MLCP

\(\text{NO}\)
Nitrergic oxide

\(\text{NO}\)
Nitrergic oxide

\(\text{NO}\)
Nitrergic oxide

\(\text{NO}\)
Nitrergic oxide

\(\text{NO}\)
Nitrergic oxide
Smooth muscle has low energy-requirement for contraction.

**Sustained contraction with little energy expenditure!**

Latch mechanism
SINGLE-UNIT (VISCERAL) SMOOCH MUSCLE

gap junctions – functional syntitium
.pacemaker cells"

Myogenic tone
- stretch may increase the activity
- transmitters of the autonomic nervous system modulate the activity

MULTI-UNIT SMOOTH MUSCLE

Spontaneously not active smooth muscle.

Autonomic nervous system innervates the muscle (BOTH stimulatory and inhibitory transmitters).

Mechanical stretch induces muscle relaxation (storage in the urinary bladder, gallbladder).

*stress relaxation*